

Protocols

Use of autologous fat grafting in reconstruction following mastectomy and breast conserving surgery: An updated systematic review protocol



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ABSTRACT

Introduction: Use of autologous fat grafting (AFG) for breast reconstructive surgery is gaining acceptance, but concerns regarding its efficacy and safety remain. We present a protocol for a systematic review that aims to update the findings since our previous systematic review on a number of outcomes of AFG.

Methods: The systematic review has been registered a priori (UIN: reviewregistry308). All study designs, including randomised controlled trials, cohort studies, case-controlled studies and case reports/series, reporting original data, on women undergoing AFG for breast reconstruction following mastectomy or breast conserving surgery, will be included. Six categorical outcomes will be assessed: oncological; clinical; aesthetic/functional; patient-reported; process; and radiological.

The search strategy will be devised to investigate 'fat grafting and breast reconstruction'. Electronic databases will be searched, 01 April 2014 to 21 August 2017: PubMed, MEDLINE®, EMBASE, SCOPUS, CINAHL, PsychINFO, SciELO, The Cochrane Library, including the Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effect (DARE), the Cochrane Methodology Register, Health Technology Assessment Database, the NHS Economic Evaluation Databases and Cochrane Groups, ClinicalTrials.gov, Current Controlled Trials Database, the World Health Organisation (WHO) International Clinical Trials Registry Platform, UpToDate.com, NHS Evidence and the York Centre for Reviews and Dissemination. Grey literature will be searched. Two trained, independent teams will screen all titles and abstracts, and relevant full texts, for eligibility. Data will be extracted under standardised extraction fields into a preformatted database.

Ethics and dissemination: The systematic review will be published in a peer-reviewed journal and presented at national and international meetings within fields of plastic, reconstructive and aesthetic surgery, and surgical oncology. The work will be disseminated electronically and in print. Brief reports of the review and findings will be disseminated to interested parties through email and direct communication. The review aims to guide healthcare practice and policy.

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1. Introduction

Breast cancer is the most common cancer in UK females, with over 50,000 new diagnoses each year in the UK [1]. The vast majority of women diagnosed with breast cancer subsequently undergo surgery with curative intent, either mastectomy or breast conserving surgery (BCS). Increasingly there is a trend towards BCS over mastectomy. Surgery is often combined with radiotherapy or chemotherapy or hormonal treatments in efforts to minimise likelihood of recurrence.

Autologous fat grafting (AFG) is a technique gaining popularity for both reconstructive and/or cosmetic indications. It involves harvesting the patient's own adipose tissue, from distant sites, and implanting this tissue to the breast. There are several advantages to this approach: the fat harvested is often in ample supply; the patient's own tissue is used; harvesting procedures generally result in minimal donor site morbidity or cosmetic disturbance; foreign body or complicated flap procedures are avoided; procedures can be performed as a day case; AFG can rejuvenate breast skin which antagonises the effects of ageing and radiotherapy [2–4].

There are several disadvantages to consider with AFG [5–9]. Obtaining consistently good cosmetic and reconstructive results,

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with lasting volume, has been a challenge. Fat is implanted into a loose and poorly vascularised space after BSC or mastectomy, which puts it at risk of necrosis. Necrotic fat can instigate an inflammatory reaction resulting in fibrosis, cyst formation, calcification or local infection [10–13]. In 1987 the American Society of Plastic and Reconstructive Surgeons (ASPRS) Ad Hoc Committee on New Procedures therefore prohibited use of AFG to the female breast [14]. Since then, there has been effort to develop techniques to improve graft take and fat maintenance [4,14]. ‘Structural fat grafting’ [10] where small aliquots of fat are transplanted through multiple tunnels in a multi-layered and multidirectional way can maximise adipocyte contact with host tissue and hence survival and incorporation [11], and has been shown to be efficacious [15]. The scarring and calcifications that can result from AFG might mask detection of breast cancer on mammography. In one sample as many as 16.7% of patients showed had microcalcification clusters after AFG [16]. The ASPS, however, have stated there appears to be no interference with breast cancer detection [13]. There are additional concerns are that adipocytes transplanted into areas of previous malignant change may directly stimulate the formation of cancer [5]. Adipocyte tissue is increasingly recognised as an endocrine organ, rich in mesenchymal stem cells (MSCs) [4]. Adipocyte derived stem cells (ADSCs) have potential to differentiate into cells including chondrocytes, osteocytes, myoblasts, and secrete angiogenic factors [17]. Promotion of angiogenesis in a tumour bed post mastectomy or BSC is of substantial oncological concern. Adipocyte tissue has an integral role in breast cancer progression and in metastasis [6]. In animal studies engrafted MSCs were less able to regulate growth patterns which could predispose to cancer [7,8]. Due to the significant potential harmful effects of AFG, in 2009 the American Society of Plastic Surgeons (ASPS) stated fat grafting was not strongly recommended by the Fat Grafting Task force due to limited scientific data on safety and efficacy [13].

The potential advantages of AFG has stimulated significant interest. It is essential to verify whether potential benefits of AFG outweigh the potential risk. In 2014 we conducted a systematic review [18] analysing the outcomes along the six dimensions of oncological, clinical, aesthetic/functional, patient-reported, process and radiological. The results of this review revealed significant heterogeneity on studies reporting on AFG outcomes in terms of techniques, patient population, indications and definitions, which precluded a meta-analysis of results. Importantly findings indicated no evidence that AFG promoted cancer recurrence or primary cancer, overall complications were low and most patients and clinicians were satisfied with the results. However, most studies included were of poor quality. Since 2014 there has been growing interest and use of AFG techniques for breast reconstruction. A basic search of the SCOPUS database for “fat grafting” and “breast reconstruction” (Fig. 1). Since the start of January 2017 to the start of August 2017, the SCOPUS search revealed that 54 articles had since been published in this area. As the use of AFG in breast reconstructive surgery is a rapidly developing area, an up-to-date systematic review and meta-analysis is needed.

2. Objectives

The primary objective is to perform an up-to-date comprehensive systematic review of AFG for breast reconstruction to determine the safety efficacy and radiological outcomes.

2.1. Primary objectives

The primary objective is to determine outcomes of AFG for breast reconstruction in women following mastectomy or BCS along 6 dimensions:

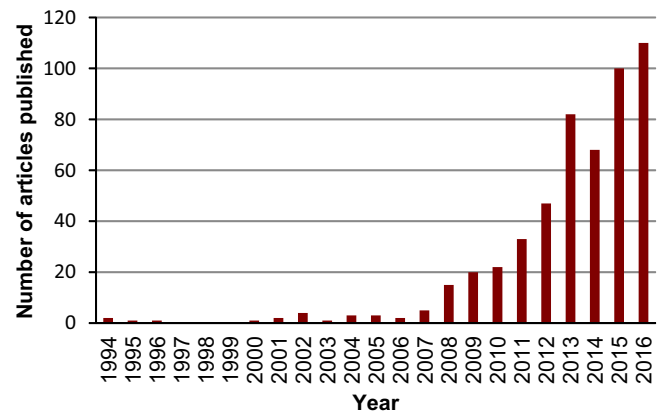


Fig. 1. Number of articles published per year and indexed by SCOPUS under the search term “fat grafting” AND “breast reconstruction”.

- (1) Oncological.
- (2) Clinical.
- (3) Aesthetic/functional.
- (4) Patient-reported.
- (5) Process.
- (6) Radiological.

2.2. Secondary objectives

The secondary objectives include

- (1) Determine optimal methods of AFG including fat harvesting, preparation and injection.
- (2) Determine the indications of AFG.
- (3) Refine the patient selection for AFG.

3. Method

This systematic review will be conducted in line with recommendations specified in the Cochrane Handbook for Intervention Reviews V.5.1.0 and is AMSTAR compliant [19] and reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [20]. This protocol has been developed a priori, and the systematic review has been registered a priori on the Research Registry® (UIN: reviewregistry308, www.researchregistry.com). The methodology will closely follow that used in the systematic review and meta-analysis in 2015 for maximum comparability [18].

4. Criteria

The following inclusion and exclusion criteria will be used to minimise heterogeneity with previous reviews and address research questions

5. Types of studies included

All original research studies, levels 1–5 of the Oxford Centre for Evidence-Based Medicine [21] (randomised controlled trials (RCTs), cohort studies, case-controlled, case series, case reports) reporting on one or more of the outcomes of interest, will be included. Unpublished data and reports will also be considered if the methodology and data are accessible. Duplicate articles, cost-effectiveness studies, studies not reporting on primary data (review articles, editorials, discussions, commentaries, letters) and studies not reporting on the indication for AFG, will be excluded.

6. Types of participants

The population of interest is all women undergoing immediate or delayed breast reconstruction following either mastectomy, quadrantectomy, wide-local-excision or lumpectomy in the treatment of breast cancer will be included. Male and transgender cases will be excluded.

7. Types of intervention

The interventions of interest include all AFG techniques used for breast reconstruction following oncological surgery. AFG may either be used for primary reconstruction (following mastectomy or BCS) or secondary reconstruction (following an initial reconstruction with implants or flaps). Studies reporting outcomes of cadaveric fat grafts or pedicled fat flaps will be excluded. Studies where AFG was used in conjunction with another reconstructive technique (such as implants or flaps) will be excluded. Studies where fat grafting is used for cosmetic breast augmentation, to reconstruct traumatic breast defects (for example after amputation, ballistic or blast trauma or burns) will be excluded. Studies where fat grafting is used as a salvage procedure for failed reconstruction or purely for nipple reconstruction will be excluded.

8. Types of comparators

Where comparative studies are included, AFG may be compared to implant-, flap-based reconstructions or no reconstruction at all.

9. Outcomes of interest

There will be six domains of outcomes of interest, defined as follows:

- (1) Oncological: defined as the incidence of new primary or recurrent breast cancer.
- (2) Clinical: defined as the incidence of intra- and post-operative complications, including local infection, fat necrosis, oil cysts, palpable nodules. Complications will be graded using the validated Clavien-Dindo classification system [22], which assesses the therapeutic consequences of complications.
- (3) Aesthetic and functional: defined both: (1) subjectively as the clinician satisfaction with the breasts, measured through either questionnaire, visual analogue or the Netscher score [23]; and (2) objectively through changes in the LENT-SOMA score [24].
- (4) Patient-reported: defined subjectively patient satisfaction with the procedure, either measured by questionnaire, visual analogue or other scales or formal instruments including the BREAST-Q [25].
- (5) Process: defined as the number of sessions required to achieve satisfactory outcomes, expressed as a mean and range for the group.
- (6) Radiological: defined as the incidence of radiological abnormalities (calcification, microcalcification, cysts and other masses) that may potentially interfere with mammographic screening

10. Search methods for identification of studies

Electronic databases will be searched from 01 April 2014 to 21 August 2017. 01 April 2014 was chosen as a start date to update literature since the search date of search of the previously published systematic review/ meta-analysis [18]. The following fifteen electronic databases will be searched: PubMed, MEDLINE®,

EMBASE, SCOPUS, CINAHL, PsychINFO, SciELO, The Cochrane Library, including the Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effect (DARE), the Cochrane Methodology Register, Health Technology Assessment Database, the NHS Economic Evaluation Databases and Cochrane Groups, ClinicalTrials.gov, Current Controlled Trials Database, the World Health Organisation (WHO) International Clinical Trials Registry Platform, UpToDate.com, NHS Evidence and the York Centre for Reviews and Dissemination.

11. Search term and keywords

The search strategy has been designed with expert input, to identify articles focused on 'fat grafting and breast reconstruction'. A search will be conducted using appropriate keywords in English combined with Boolean logical operators as follows: lipostructuring OR lipotransfer OR lipomodelling OR lipomodelling [Title/Abstract] OR "adipose tissue/transplantation" [MeSH Terms] OR fat OR "autologous fat" OR "adipose tissue" OR "body fat" OR "tissue adipose" OR "fatty tissue" [Title/Abstract] OR "adipose tissue" [MeSH Terms] AND (autograft* OR auto-transplant* OR graft* OR transplant OR transplantat* OR injection OR transfer OR lipofilling [Title/Abstract]) AND (mammoplast* OR mammaplast* [Title/Abstract]) OR "mammaplasty" [MeSH Terms] OR ("breast reconstruction" OR "breast reconstructed" OR "breast augmentation" OR "breast enlargement" OR "breast surgery" [Title/Abstract]), adapted to the appropriate syntax of each database. An example of the search strategy used on MEDLINE is shown in Table 1.

Articles will not be excluded based on publication status. The search will not be limited to articles written in English. Articles written in a non-English language can proceed to abstract screening (since the abstract will be in English), and if full-text is required to determine eligibility the authors of the manuscript will firstly be contacted to ask for an English translation, if this is not possible a native speaker will be asked to translate, if this is not possible Google translate (Google, Mountain View, California, USA), a recognised as an approach to minimise language bias in systematic reviews [26], will be used.

12. Searching other resources

The grey literature will also be searched. Open Grey <http://www.opengrey.eu> will be searched. The references of all included

Table 1
An example of a preliminary MEDLINE® conducted on 2nd August 2017.

Search number	Search	Studies generated
1	Mammaplasty/	9715
2	((breast adj2 reconstruct*) or mammaplast* or (breast adj2 conserv* surg*)),ti,ab.	14,151
3	1 or 2	18,182
4	Transplantation, Autologous/ and Adipose Tissue/	1034
5	Adipose Tissue/tr [Transplantation]	3023
6	Adipose Tissue/ and Tissue Transplantation/	92
7	(autologous and ((fat* or adipos*) adj5 (graft* or transplant* or transfer* or inject*))),ti,ab.	1732
8	((fat* or adipos*) and (graft* or transplant* or transfer* or inject*)),ti.	5978
9	((autograft* or autotransplant*) adj3 (fat* or adipos*)),ti,ab.	120
10	(lipostructur* or lipomodel* or lipofill* or lipotransfer* or lipotransplant* or lipo-structur* or lipo-model* or lipo-fill* or lipo-transfer* or lipo-transplant*)),ti,ab.	517
11	4 or 5 or 6 or 7 or 8 or 9 or 10	8444
12	3 and 11	548
13	limit 12 to yr="2014 -Current"	257

papers and prior systematic reviews will be searched for any relevant studies that were not already captured through our search. The Conference proceedings from the ACS and ASPS Annual Congresses in 2012 and the European Plastic Surgery Research Council (EPSRC) Annual Meetings of 2012 and 2013 will be searched to capture recent as yet unpublished studies. Researchers actively contributing to this field will be identified from published articles 'author of correspondence' and will be contacted directly to ask about further published or unpublished studies. The link to the PROSPERO record for the protocol will be advertised on the lead author's Twitter account to call for unpublished work made.

13. Identification and selection of studies

The articles identified from the electronic and manual searches will be recorded into a Microsoft Excel 2017 database and duplicates excluded (Microsoft, Redmond, Washington, USA), along with the citation, titles and abstract.

Two trained teams, acting independently, will screen articles for inclusion in two stages.

- (1) Titles and abstract.
- (2) Full text.

Any discrepancies at each stage will be resolved by consensus to reach a final agreed list of articles. If consensus cannot be resolved a senior author with arbitrate. The full text will also be reviewed for any articles where doubt over inclusion exists after review of the title and abstract. Multiple reports of the same study will be linked together. If necessary authors may be contacted to clarify study eligibility, results, or to access an article. Articles that meet inclusion criteria will proceed to data extraction.

14. Data extraction, collection and management

Data extraction will be performed by two teams, acting independently, with discrepancies resolved by consensus, or senior author arbitration. Data will be input into a preformatted Microsoft Excel 2017 database (Microsoft, Redmond, Washington, USA) under standardised extraction fields to facilitate easy and consistent data entry. The same extraction fields will be used to those in the previous systematic review [18] to enable a comparison and synthesis of results. The following data will be extracted:

- (1) Article demographics: name, country and year of publication.
- (2) Study design and level of evidence according to Oxford Centre for Evidence-based medicine.
- (3) Conflicts of interest and funding.
- (4) Number of participants.
- (5) Number of breasts treated.
- (6) Age of participants, expressed as mean or median with ranges, where reported.
- (7) Previous oncological surgery: mastectomy, quadrantectomy, lumpectomy or wide-local excision.
- (8) Prior adjuvant radiotherapy.
- (9) Previous breast reconstruction procedure(s).
- (10) Time interval between oncological surgery.
- (11) Donor site(s) used.
- (12) Techniques: recipient site preparation, graft harvest, preparation and injection.
- (13) Mean volume of fat injected per breast.
- (14) Mean follow-up length.
- (15) Loss to follow-up expressed as a percentage.

- (16) Oncological, clinical, aesthetic/functional, patient-reported, process and radiological outcomes as defined above.

15. Data analysis

The outcomes of interest will be tabulated. Basic descriptive statistics including weighted means, ranges and standard deviations of the mean will be used to provide appropriate summary of the data. Review Manager V.5.2.6 (RevMan) [27] will be used to assess the heterogeneity of comparative studies (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan) Version 5.2. 2012). If the heterogeneity is substantial, defined by the Inconsistency Index (I^2) of >75% [28], a meta-analysis will not be conducted. Results will be both compared and synthesised in additional analyses with those from the previous systematic review conducted by our group [18].

16. Subgroup analysis

Additional analyses will be conducted to separate AFG used for total breast reconstructions post-mastectomy and AFG used to correct contour deformities post-implant, flap-based reconstructions or BCS alone.

17. Assessment of bias

The Grading of Recommendation Assessment, Development and Evaluation (GRADE) system [19,27] will be used to assess the methodological quality of included studies. The GRADE system offers four levels of evidence: high; moderate; low; very low. RCTs are considered highest level of evidence. Case series and case reports are 'very low'. Quality may be downgraded along five domains: (1) Study design or implementation limitations; (2) Inconsistency in results; (3) Indirectness of evidence; (4) Imprecision of estimates; and (5) Publication bias. Quality may be upgraded because of three domains: (1) A very large magnitude of effect; (2) A dose-response gradient; (3) All plausible biases would reduce an apparent treatment effect. For RCTs it will be documents: (1) whether or not clinically relevant outcomes are reported; (2) whether results are comparable with protocols and subsequent publications where available. Key missing information across all study types such as complication rates and follow-up times will be documented and assessed.

18. Dissemination

This systematic review will provide a comprehensive up-to-date evaluation of the use of AFG for breast reconstruction. Results have the potential to influence the management of patients with breast cancer postmastectomy or BCS and the reconstructive options offered to them. Results from this systematic review, alongside the previously reported findings in the literature, will lead to conclusions and recommendations for clinicians, researchers, plastic surgical societies and policy makers. The manuscript will be published in English in a peer-reviewed journal. The authors will respond to any commentary generated. The findings will be presented at national and international meetings within the fields of plastic, reconstructive and aesthetic surgery, general surgery and surgical oncology. The work will be disseminated electronically and in print to leading researchers in the field. Brief reports of the review findings will be disseminated directly to the appropriate audiences and societies through email and other modes of communication. Updates of the review could be conducted to inform and guide healthcare practice and policy should

the need arise. Authors of position statements and guidelines relating to AFG will be informed of the results directly.

Ethical approval

In line with guidance issued jointly by INVOLVE and the National Research Ethics Service (NRES) ethical approval is not needed for systematic reviews, even ones which involve patients and members of the public in a planning and advisory capacity (INVOLVE. Patient and public involvement in research and research ethics committee review, 2009).

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Contributions

RAA – concept, writing, protocol approval.
MRB – writing protocol.
ND – writing protocol.
MFB – writing protocol.
SF – writing protocol.
TO – writing protocol.
DPO – concept and final protocol manuscript approval.

Conflict of interests

None.

Guarantor

Riaz A. Agha.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.isjp.2017.08.003>.

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